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Technical Report #21

"Chromatographic Assessment of Hydrogen-Bond Donating Ability

by

R. Wanke, M.C. Etter, and P.W. Carr

**University of Minnesota
Department of Chemistry
Minneapolis, MN**

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Hydrogen bonds are strong orienting forces in the organic solid state. A general heuristic principle that has guided our cocrystallization studies is "the best hydrogen-bond donor hydrogen bonds to the best hydrogen-bond acceptor".¹ Successive hydrogen-bond donors, barring severe conformational or crystal packing constraints, hydrogen bond to available acceptors in rank order. Therefore an a priori knowledge of the relative hydrogen-bond strength of the hydrogen-bonding groups within a given cocrystal should allow for the prediction of the hydrogen-bond connectivity pattern in the solid state.

Within our laboratory, Taft β values² have been used to assess the hydrogen-bond basicity and pKa values have been used to estimate the hydrogen-bond acidity of compounds or specific functional groups within a cocrystal pair. No general correlation exists between pKa and the free energy of hydrogen-bond association across different families of hydrogen-bond donors; therefore, the use of pKa to assess the relative hydrogen-bond acidity of donors is prone to inaccuracy. Relative scales of hydrogen-bond acidity such as the α_2^H scale³, which have been derived from the free energies of hydrogen-bond association in carbon tetrachloride, do exist. However, tabulations of α_2^H are less extensive than β and do not include solid compounds of prime interest in cocrystallization studies. Therefore, chromatography was selected as a potential empirical method to assess the hydrogen-bond acidity of hydrogen-bond donor compounds used in cocrystallization studies.

In chromatography, small differences in molecular interaction between a solute for the stationary and mobile phases result in macroscopic differences in chromatographic retention. The logarithm of the chromatographic capacity factor ($\log k'$) is proportional to the free energy of partitioning of the solute from the mobile phase into the stationary phase and as such, accounts for specific hydrogen-bonding interactions and van der Waal's interactions of the solute with the stationary or mobile phase. In order to isolate the hydrogen-bonding contribution to the retention, two LC approaches were devised that involve comparing the retention of a given solute on two matched stationary phases or on two matched mobile phases, respectively. The columns and mobile phases for the two different approaches are carefully selected to be matched in their nonhydrogen-

¹ Etter, M.C. *J. Phys. Chem.* 1991, 95, 4601.

² Kamlet, M.J.; Abboud, J.-L. M.; Abraham, M.H.; Taft, R.W. *J. Org. Chem.* 1983, 48, 2877.

³ Abraham, M.H.; Grellier, P.L.; Prior, D.V.; Duce, P.P.; Morris, J.J.; Taylor, P.J. *J. Chem. Soc., Perkin Trans. 2* 1989, 699.

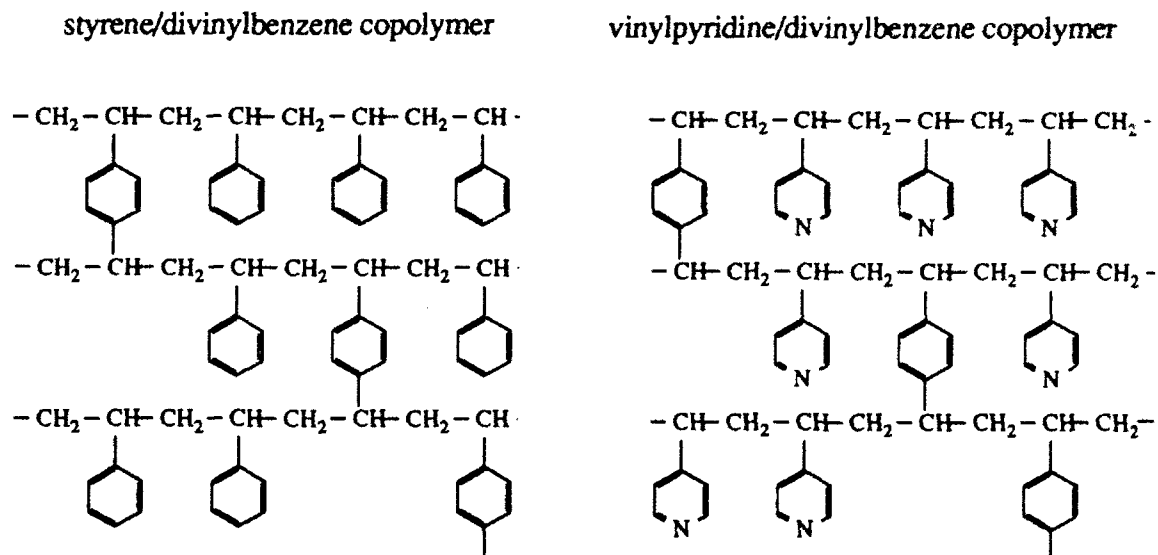
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bonding properties but different in their hydrogen-bond accepting abilities. As shown in Scheme 1, two polymeric columns, a poly(vinylpyridine-divinylbenzene) column and a poly(styrene-divinylbenzene) column, along with a 90:10 acetonitrile/dimethylsulfoxide mobile phase are implemented for the dual column approach. For the dual mobile phase approach, solutes are chromatographed on the poly(vinylpyridine-divinylbenzene) column using two binary mobile phases, a 95:5 acetonitrile/triethylphosphate and a 80:20 acetonitrile/triethylphosphate mobile phases.

Scheme I



Both approaches were critically evaluated to see if the difference in the logarithm of the capacity factors ($\Delta \log k' \equiv$ "comparative retention") on the dual columns or dual mobile phases was a linear function solely of the hydrogen-bond acidity of the solute. The contribution to the measured $\Delta \log k'$ for each of the various factors that influence retention, such as solute size ($V_2/100$), dipolarity (π_2^*), polarizability (δ_2), hydrogen-bond acidity (α_2) and hydrogen-bond basicity (β_2), was investigated by chromatographing selected series of compounds. The influence of solute size on the

comparative retention was discerned by chromatographing a 4-alkylaniline homologous series. The effect of solute dipolarity and solute hydrogen-bond basicity was investigated by chromatographing a series of hydrogen-bond acceptor-only compounds that covered a wide range of dipolarity and hydrogen-bond basicity. The effect of solute polarizability was evaluated by chromatographing a series of polycyclic aromatic compounds. The dependence of the comparative retention on hydrogen-bond acidity was tested by chromatographing compounds ranging in acidity from aniline to p-nitrophenol.

For each test series of compounds, linear regression analysis was performed to determine the multiplicative coefficient for the parameter being probed. Multiple linear regression analysis was used to determine the coefficients for those series of compounds in which more than one factor was being probed and statistical tests on the regression variance were used to determine the statistical validity of the effect of each factor on $\Delta \log k'$. Values for the various solute parameters - $V_2/100$, π_2^* , δ_2 , α_2 , and β_2 - were taken from the literature.⁴ Since the solute parameter sets each cover the same range of values, direct comparison of the parameter coefficients allows for the assessment of the dependence of each factor on the comparative retention. As shown in Table I, for both approaches the solute hydrogen-bond acidity had the greatest effect on the comparative retention. However, the $\Delta \log k'$ values determined from the dual mobile phase approach were less influenced by the solutes' nonhydrogen-bonding attributes and therefore, provide a purer measure of the solute hydrogen-bond acidity. Principle component analysis of the dual mobile phase $\Delta \log k'$ data for the hydrogen-bond donors indicates that over 99.9% of the variance is explained by one explanatory variable, which from the experimental results can be assigned to the solute hydrogen-bond acidity.

⁴ (a) Bondi, A. *J. Phys. Chem.* 1964, 68, 441. (b) Li, J.; Zhang, Y.; Dallas, A.J.; Carr, P.W. *J. Chrom.* 1991, 550, 101-134. (c) Kamlet, M.J.; Doherty, R.M.; Abraham, M.H.; Marcus, Y.; Taft, R.W. *J. Phys. Chem.* 1988, 92, 5244 - 5255. (d) Abraham, M.H.; Grellier, P.L.; Prior, D.V.; Duce, P.P.; Morris, J.J.; Taylor, P.J. *J. Chem. Soc., Perkin Trans. 2* 1989, 699-711. (e) Abraham, M.H.; Grellier, P.L.; Prior, D.V.; Morris, J.J.; Taylor, P.J. *J. Chem. Soc., Perkin Trans. 2* 1990, 521-529.

Table I
Dependence of the $\Delta \log k'$ Values on Various Solute Parameters

Solute Parameter	<u>Matched Stationary Phases</u>		<u>Matched Mobile Phases</u>	
	<u>Coefficient</u>	<u>Relative Value</u>	<u>Coefficient</u>	<u>Relative Value</u>
α_2	1.6	1.00	0.78	1.00
β_2	0.061	0.039	†	†
π_2^*	0.19	0.12	-0.051	0.065
δ_2	0.61	0.38	0.10	0.13
$V_2/100$	-0.78	0.49	0.18	0.23

† insignificant dependence on this variable as deemed by the Ehrenson F test.⁵

Currently, experiments are underway to utilize the dual mobile phase approach to assess the hydrogen-bond acidity of various hydrogen-bond donors used in cocrystallizations. Specific attention will be given to see if the expected hydrogen-bond associations based on the solute's measured hydrogen-bond acidity occur in the solid state.

⁵ Ehrenson, S. *J. Org. Chem.* 1979, 44, 1793-1797.

ORGANIC CHEMISTRY & MOLECULAR RECOGNITION - Distribution List

Professor O.T. Beachley, Jr.
Department of Chemistry
State University of New York
Buffalo, NY 14214

Dr. Alan Berry
Chemistry Division, Code 6120
Naval Research Laboratory
4555 Overlook Avenue, SW
Washington, DC 20375-5000

Professor Jerald S. Bradshaw
Department of Chemistry
Brigham Young University
Provo, UT 84602
R&T Code 413p002

Professor Ronald Breslow
Department of Chemistry
Columbia University
New York, NY 10027
R&T Code 413p005

Dr. Duncan W. Brown
Advanced Technology Materials, Inc.
520-B Danbury Road
New Milford, CT 06776

Professor Herbert C. Brown
Purdue University
Department of Chemistry
West Lafayette, IN 47907

Professor Steven L. Buchwald
Department of Chemistry
Massachusetts Institute of Tech
Cambridge, MA 02139

Professor Cynthia J. Burrows
Department of Chemistry
State University of New York at
Stony Brook
Stony Brook, NY 11794-3400

Dr. Roque J. Calvo
Executive Secretary
The Electrochemical Society
10 South Main Street
Pennington, NJ 08534-2896

Professor Peter Chen
Department of Chemistry
Harvard University
Cambridge, MA 02138

Professor N. John Cooper
Department of Chemistry
University of Pittsburgh
Pittsburgh, PA 15260

Professor Anthony W. Czarnik
Department of Chemistry
Ohio State University
120 West 18th Avenue
Columbus, OH 43210-1173

Professor Peter Dervan
Department of Chemistry
California Institute of Technology
Pasadena, CA 91125

Professor Francois N. Diederich
Department of Chemistry
University of California
405 Hilgard Avenue
Los Angeles, CA 90024

Professor Dennis A. Dougherty
Department of Chemistry
California Institute of Technology
Pasadena, CA 91125

Professor Kenneth M. Doxsee
Department of Chemistry
University of Oregon
Eugene, OR 97403

Dr. Regis J. Ebner, Jr.
Director of Finance
Materials Research Society
9800 McKnight Road, Suite #27
Pittsburgh, PA 15237

Professor Margaret C. Etter
Department of Chemistry
University of Minnesota
207 Pleasant Street, S.E.
Minneapolis, MN 55455

Professor Wilmer K. Fife
Department of Chemistry
Indiana University
1125 East 38th Street
P.O. Box 647
Indianapolis, IN 46223

Professor Samuel H. Gellman
Department of Chemistry
University of Wisconsin
Madison, WI 53706

Professor Andrew D. Hamilton
Department of Chemistry
University of Pittsburgh
Pittsburgh, PA 15260

Prof. Mark J. Hampden-Smith
Department of Chemistry
University of New Mexico
Albuquerque, NM 87131

Professor William E. Hatfield
Department of Chemistry
University of North Carolina
Chapel Hill, NC 27514

Dr. Kelvin Higa
Chemistry Division
Research Department
Naval Weapons Center
China Lake, CA 93555

Professor Kenneth D. Karlin
Merryman Hall 146
The Johns Hopkins University
34th & Charles Streets
Baltimore, MD 21218

Professor Arthur E. Martell
Department of Chemistry
Texas A&M University
College Station, TX 77843-3255

Professor Thomas J. McCarthy
Department of Polymer Science
University of Massachusetts
Room 701 Graduate Research Center
Amherst, MA 01003
R&T Code 400x015

Dr. Stephen W. McElvany
Code 6113, Chemistry Division
Naval Research Laboratory
Washington, DC 20375-5000

Professor Lisa McElwee-White
Department of Chemistry
The Leland Stanford Junior Univ.
Stanford, CA 94305

Professor Theodore G. Pavlopoulos
Naval Ocean Systems Center
Code 521 (B-111)
San Diego, CA 92152-5000

Professor William S. Rees, Jr.
Chemistry Division
The Florida State University
Tallahassee, FL 32306-3006

Professor Peter Schultz
Department of Chemistry
University of California
Berkeley, CA 94720
R&T Code 413j005

Dr. Alok Singh
Ctr. for Bio/Molec. Science Eng.
Department of the Navy
Naval Research Lab., Code 6090
Washington, DC 20375-5000

Dr. Michael L. Sinnott
University of Bristol
School of Chemistry
Cantock's Close
Bristol, England BS8 1TS

Dr. Timothy M. Swager
Department of Chemistry
University of Pennsylvania
Philadelphia, PA 19104-6323

Professor Richard L. Wells
Department of Chemistry
Duke University
Durham, NC 27706

Professor Jeffrey D. Winkler
Department of Chemistry
The University of Chicago
5735 S. Ellis Avenue
Chicago, IL 60637

Professor Jeffrey D. Zubkowski
Department of Chemistry
Jackson State University
P.O. Box 17910, 1400 Lynch St.
Jackson, MS 39217